

real post-myocardial infarction edema reaction. We respectfully disagree with Dr. Zhang and colleagues on their comment regarding the inappropriateness to draw the conclusion from our work that the second wave is also developed by edematous reaction. Indeed, we demonstrated that T₂ abnormalities and, more importantly, increased water content in the ischemic region, as measured by the gold standard desiccation technique, were ultimately as high at day 7 as that documented at early reperfusion. Definitely, the quantification of the myocardial water content by reference standards was crucial for demonstrating a consistent appearance of 2 consecutive waves of real edema during the first week after ischemia/reperfusion in our experimental study.

Dr. Zhang and colleagues point out that salvageable and infarct regions might follow disparate edema evolution patterns. From the cardiac magnetic resonance point of view, we agree that placing a region of interest in the full thickness of the left ventricular wall is troublesome as it will contain different myocardial states. However, the identification of “clean” regions clearly outside hemorrhage/microvascular obstruction areas may be extremely difficult and, more importantly, may be subjected to a big source of bias. The quantification of water content by reference standard in such small regions would be even more difficult to perform as this procedure needs to be done in a rapid and careful manner, avoiding tissue manipulation as much as possible. We tend to disagree with the idea that edematous and infarcted zones are equivalent to salvageable and hemorrhagic areas, respectively, as suggested by Dr. Zhang and colleagues. In any case, we believe that the possibility of including different myocardial states had little effect on the results reported in our work given that transmural extent of infarction was >80% in all evaluated segments containing the regions of interest, and the observed parallel course of T₂ relaxation times and water content.

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REFERENCES

1. Fernández-Jiménez R, Sánchez-González J, Agüero J, et al. Myocardial edema after ischemia/reperfusion is not stable and follows a bimodal pattern: imaging and histological tissue characterization. *J Am Coll Cardiol* 2015;65:315-23.
2. Verhaert D, Thavendiranathan P, Giri S, et al. Direct T2 quantification of myocardial edema in acute ischemic injury. *J Am Coll Cardiol Img* 2011;4:269-78.
3. Kloner RA. New observations regarding post-ischemia/reperfusion myocardial swelling. *J Am Coll Cardiol* 2015;65:324-6.
4. Croisille P, Kim HW, Kim RJ. Controversies in cardiovascular MR imaging: T2-weighted imaging should not be used to delineate the area at risk in ischemic myocardial injury. *Radiology* 2012;265:12-22.

Myocardial Salvage, Area at Risk by T2w CMR



The Resolution of the Retrospective Radio Wave Paradigm?

In 2006, in an editorial published in a fellow journal by Pennell (1) T₂-weighted (T2w) cardiac magnetic resonance (CMR) imaging was presented as a promising method to retrospectively assess the myocardial area at risk. The area at risk could be reliably measured by contouring the myocardial edema using T2w sequences. The combination with late gadolinium-enhanced myocardial volume assessed during the same examination allowed the final infarct size measurement, and from there the simple and powerful concept of myocardial salvage was issued (2). Since then, numerous trials assessing new reperfusion strategies have used the salvage index as a clinical endpoint (3).

With this in mind, we read with great interest in the *Journal*, the paper by Fernández-Jiménez et al. (4). These investigators, relying on very solid and consistent work, unveil very new findings. They show with striking results that myocardial edema after ischemia reperfusion is highly variable and follows a bimodal pattern. These findings are novel and challenge the accepted view on the development of edema after an ischemic insult. In our opinion, these findings also significantly question the accepted view of T2w CMR as a reliable tool to assess the area at risk, and thus the myocardial salvage index, which we had already challenged recently (5).

Although the investigators are very cautious about this topic in their paper, we would value their opinion on this debated issue of CMR retrospective accuracy to assess the area at risk. Also, considering that these investigators have used the myocardial salvage index as an endpoint in a previous trial (3), we would

appreciate their opinion on the use of such an index in the light shed by their paper.

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REFERENCES

1. Pennell D. Myocardial salvage: retrospection, resolution, and radio waves. *Circulation* 2006;113:1821-3.
2. Friedrich MG, Abdel-Aty H, Taylor A, Schulz-Menger J, Messroghli D, Dietz R. The salvaged area at risk in reperfused acute myocardial infarction as visualized by cardiovascular magnetic resonance. *J Am Coll Cardiol* 2008;51:1581-7.
3. Ibanez B, Macaya C, Sánchez-Brunete V, et al. Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial. *Circulation* 2013;128:1495-503.
4. Fernández-Jiménez R, Sánchez-González J, Agüero J, et al. Myocardial edema after ischemia/reperfusion is not stable and follows a bimodal pattern: advanced imaging and histological tissue characterization. *J Am Coll Cardiol* 2015;65:315-23.
5. Mewton N, Rapacchi S, Augeul L, et al. Determination of the myocardial area at risk with pre- versus post-reperfusion imaging techniques in the pig model. *Basic Res Cardiol* 2011;106:1247-57.

REPLY: Myocardial Salvage, Area at Risk by T2w CMR



The Resolution of the Retrospective Radio Wave Paradigm?

We appreciate the interest and comments from Dr. Mewton and colleagues about our recently published work (1). In the context of myocardial infarction (MI), tissue edema appears initially in the form of cardiomyocyte swelling during the early stages of ischemia and is then significantly exacerbated on restoration of blood flow to the ischemic region (2). The relationship between MI and disturbed cardiac magnetic resonance (CMR) T₂ was initially reported 3 decades ago. However, the potential correlation between the extent of post-MI altered T₂-weighted CMR imaging and the actual area at risk (AAR) was not proposed until 2006 (3). After this initial in vivo report, the extent of post-MI T₂ CMR alteration has

been exponentially used to quantify the extent of AAR, assuming its accuracy in this regard. For many years, the post-MI edematous reaction was assumed to appear early after ischemia/reperfusion and to persist in stable form for at least 1 week. Our recent report on the post-ischemia/-reperfusion bimodal edema phenomenon (1) disrupts this classical view and calls for revisiting the assumptions described here.

Dr. Mewton and colleagues raise a highly relevant issue: What are the implications of our findings for the retrospective AAR (and myocardial salvage) quantification? Given that myocardial edema fluctuates during the first week after MI, it seems intuitive to argue that CMR-based AAR quantification will vary during the initial days after reperfusion, yet this is to be formally proven. Our data suggest that the use of CMR-based surrogate markers of infarct size (i.e., normalized to AAR) in clinical trials evaluating the effect of cardioprotective therapies, while interesting to reduce sample size, is a risky business. This call of warning is not new, and has been previously proposed by other investigators (including Dr. Mewton and colleagues), and our work supports this precaution. Please note, given the controversy in the field, in our recently published METOCARD-CNIC (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction) trial, we intentionally chose total infarct size as the primary endpoint, having salvage index as a secondary analysis (4,5).

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REFERENCES

1. Fernández-Jiménez R, Sánchez-González J, Agüero J, et al. Myocardial edema after ischemia/reperfusion is not stable and follows a bimodal pattern: imaging and histological tissue characterization. *J Am Coll Cardiol* 2015;65:315-23.
2. Kloner RA. New observations regarding post-ischemia/reperfusion myocardial swelling. *J Am Coll Cardiol* 2015;65:324-6.
3. Aletras AH, Tilak GS, Natanzon A, et al. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. *Circulation* 2006;113:1865-70.